RADIATION RESEARCH **144,** 329–341 (1995)

Errors in Exposure Assessment, Statistical Power and the Interpretation of Residential Radon Studies

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Lubin, J. H., Boice, J. D., Jr. and Samet, J. M. Errors in Exposure Assessment, Statistical Power and the Interpretation of Residential Radon Studies. *Radiat. Res.* **144,** 329–341 (1995).

To date, epidemiological studies of risk from residential radon have not convincingly demonstrated an association with lung cancer. These case-control studies, however, have inherent limitations due to errors in estimates of exposure to indoor radon. These errors take on special significance because the level of residential risk predicted from studies of underground miners is relatively low and possibly at the limit detectable by current epidemiological methods. To illustrate the problem caused by errors in exposure assessment, a series of case-control studies were simulated and resulting dose–response relationships evaluated. For each of four assumed error distributions for exposure to radon progeny, 10 indoor radon studies of 700 cases and 700 controls were generated randomly from a population with a risk of radon-induced lung cancer based on extrapolations from studies of underground miners. When exposures were assumed as known without error, 6 of 10 studies failed to find a significant dose response, in accord with the theoretical power of the study of 0.47. For simulations in which exposures were measured with error, the situation was worse, as the power of the study was reduced further and it was even less likely that a single study would result in a significant finding. For each error scenario, combining data from the 10 simulated studies did result in a significant dose response. However, the pooled results are somewhat misleading, because the effects of mobility, missing radon measurements, residential occupancy and potential confounding variables such as cigarette smoking were not taken into account. Empirical estimates of power were computed using 1,000 simulated case-control studies. When mobility and missing radon measurements in prior homes were incorporated into the design, the power of the study decreased, reducing the chance of detecting a significant effect of exposure. Enlarging study size to 2,000 cases and 2,000 controls increased the power of the study to 0.90 when exposure error was absent and subjects lived in one home only, but power was below 0.40 under realistic conditions for exposure error and mobility. When studies were generated under an assumption that exposure does not increase risk, up to 15% of simulated studies with 700 cases and 700 controls resulted in an estimated dose–response parameter in excess of the dose response from studies of miners. With increasing mobility and exposure error, it became virtually impossible to distinguish between the distributions of risk estimates from simulated studies based on an underlying excess relative risk of 0.015/working level month from estimates based on no risk from exposure. This exercise reveals the substantial contribution that errors in exposure assessment and incomplete measurements must play in explaining the inconsistency of current residential radon studies and highlights the intrinsic difficulty with such studies. Further, these simulations imply that it is unlikely that case-control studies alone will be able to determine precise estimates of risk from indoor radon, and that even future efforts at pooling epidemiological studies may not adequately address issues of risk from residential radon exposure.

INTRODUCTION

Epidemiological case-control studies reported to date have not uniformly shown an association between residential exposure to radon and its decay products and lung cancer risk, even though studies of underground miners exposed to radon, as well as experimental studies in animals, have conclusively shown that radon causes lung cancer *(1–3).* Some have interpreted this seeming inconsistency as evidence that (1) exposure to radon progeny at the levels typically found in homes does not cause lung cancer, (2) exposure to radon progeny in homes causes lung cancer but not to the extent estimated from risk models based on miners, or (3) risk among miners is dominated by smoking or by other exposures in mines and risk models based on miners are therefore not applicable to residential exposures. The inconsistency of results has led to claims that indoor radon may not pose a significant health hazard to the general population and that current approaches to risk management cannot be justified *(4, 5).* To assess these concerns, we have explored the potential for published studies and those in progress to resolve the persistent controversy concerning the risk from indoor radon.

In this paper, we show that the data from published case-control studies support a wide range of risks of residential

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TABLE I
Summary of the Seven Principal Lung Cancer Case-Control Studies, Based on Long-Term Measurements of Indoor Radon Concentration

Study/site	Subjects	Radon concentration[a]	Radon extremes	Summary of overall results
Winnipeg, Canada (*8*)	Females: 250 cases and 250 controls; males: 488 cases and 488 controls	Means of 120 and 200 Bq m^{-3} for bedrooms and basements	24% >44 Bq m^{-3}	Categories (estimated) <72, 72–144, 145–287, ≥288 Bq m^{-3} with RRs 1.0, 1.0, 0.8, 1.0 using bedroom and 1.0, 0.8, 0.9, 0.6 using basement measurements
Shenyang, China (7)	Females: 308 cases and 362 controls	Median of 85 Bq m^{-3}	20% >148 Bq m^{-3}	Categories <74, 74–147, 148–295, ≥296 Bq m^{-3} with RRs 1.0, 0.9, 0.9, 0.7
Finland (footnote 1)	Males: 238 cases and 434 controls	Mean of 211 Bq m^{-3}	40% >174 Bq m^{-3}	Quintile categories <80, 80–126, 127–173, 174–274, ≥275 Bq m^{-3} with RRs 1.0, 1.1, 1.7, 1.9, 1.1. *P* value for test of trend >0.05
Stockholm, Sweden (*10*)	Females: 210 cases and 191 hospital and 209 population controls	Mean of 128 Bq m^{-3}	28% >150 Bq m^{-3}	Categories <75, 75–110, 111–150, 151 Bq m^{-3} with RRs 1.0, 1.2, 1.3, 1.7. *P* value for test of trend 0.05. No trend after adjustment for residential occupancy or BEIR IV weighting of exposure[b]
Sweden (9)	Males and females: 1,281 cases and 2,576 controls	Mean of 107 Bq m^{-3}	25% >117 Bq m^{-3}	Categories ≤50, 50–80, 80–140, 140–400, >400 Bq m^{-3} with RRs 1.0, 1.1, 1.0, 1.3, 1.8. *P* value for test of trend <0.05
Missouri (*6*)	Female nonsmokers: 538 cases, 1,183 controls	Mean of 67 Bq m^{-3} for cases and for controls	7% >148 Bq m^{-3}	Quintile categories <30, 30–43, 44–62, 64–91, ≥91 Bq m^{-3}, with RRs 1.0, 1.0, 0.8, 0.9, 1.2
New Jersey (*11, 12*)	Females: 433 cases and 402 controls	Median of 22 Bq m^{-3}	1% >148 Bq m^{-3}	Categories <37, 37–73, 74–147, ≥148 Bq m^{-3} with RRs 1.0, 1.1, 1.3, 4.2. *P* value for test of trend 0.04; highest category had 6 cases and 2 controls
Pooled analysis: New Jersey, Shenyang, Stockholm (*13*)	Females: 966 cases and 1,158 controls[c]	See above radon information	14% >148 Bq m^{-3}	Categories <19, 19–36, 37–73, 74–110, 111–147, ≥148 Bq m^{-3}, with RRs 1.0, 1.1, 1.0, 1.0, 1.2, 1.1, after adjustment for several factors

[a]Most studies used 1-year measurements as the principal source of exposure data. The Swedish study used 3-month winter measurements, and the Finnish used 2-month winter measurements. The New Jersey and Stockholm studies used measurements of less than 1 year's duration for 9% and 13% of subjects, respectively.

[b]Residential exposures were weighted with exposures 5–15 years prior to the index date given full weight and ≥15 years before given half weight.

[c]Number of subjects differs from total of three studies due to exclusions as a consequence of a uniform definition of exposure period.

exposure to radon progeny, from as low as no effect at all to an effect greater than predicted by miner studies. Using computer simulations, we document that: (1) because the average risk from indoor radon is small, random variation alone can produce statistically significant positive associations between radon concentration and lung cancer when none exists and also non-significant associations when a miner-based level of risk is assumed; (2) the degree of consistency in studies reported to date is compatible with the consequences of population mobility, mis-specification of cumulative radon-progeny exposure and the inability to measure radon levels accurately in past residences; and (3) even large study sizes may be inadequate to quantify risk from residential radon exposures.

CASE-CONTROL STUDIES OF INDOOR RADON

To date, seven major case-control studies of lung cancer and residential radon, which have included direct measurements of indoor radon concentrations[1] *(6–12)*, and one combined analysis of three of the studies *(13)* have been published (Table I, and ref. *14)*. Numbers of lung cancers in the studies ranged from 210 to 1,281 and total over 3,800 cases. Mean or median radon concentrations in homes ranged from 22 to 220 Bq m^{-3}. Results were presented as relative risks (RR) by categories of radon level, computed as the time-weighted mean radon concentration in current and previous homes. Figure 1 shows RRs for seven residential studies by categories of Bq m^{-3}, with the lowest level serving as the referent category, and the estimated RRs extrapolated from the studies of miners included in the BEIR IV model *(2)*, adjusted to reflect residential radon concentrations and occupancy patterns *(14)* and to pass through the midpoint of

[1]E, Ruosteenoja, *Indoor Radon and Risk of Lung Cancer: An Epidemiological Study in Finland.* Doctoral Dissertation, Department of Public Health, University of Tampere, 1991.

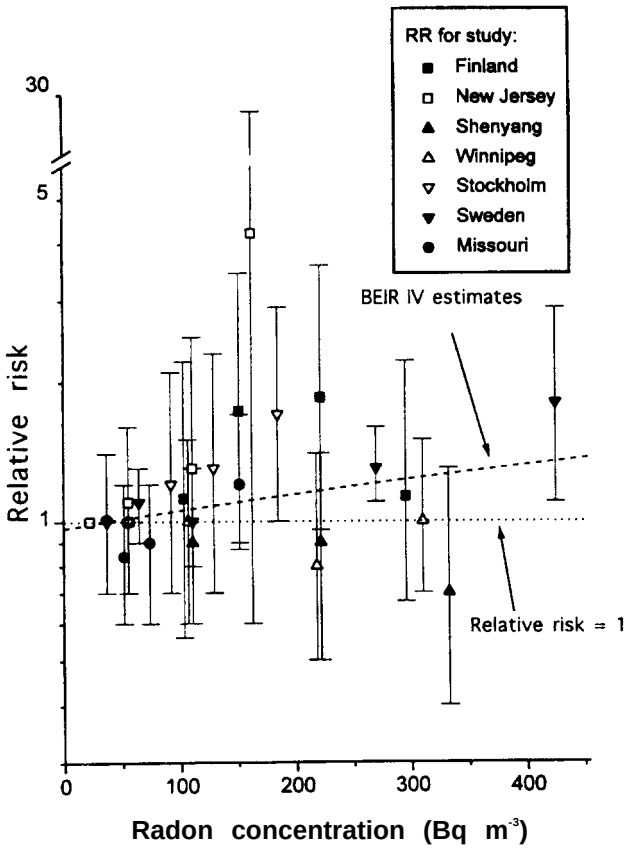


FIG. 1. Relative risk (RR) of lung cancer by categories of Bq m^{-3} for seven residential radon case-control studies. Also shown are extrapolated RRs for residential exposures from ages 35–65 years using the BEIR IV model *(2)* and an RR of 1.

the lowest exposure category. The results of the individual studies are mixed and support a wide range of potential risks from residential radon exposure, from consistency with estimates from studies of the miners to no risk at all.

The failure of the epidemiological studies to confirm unambiguously the predicted risk of radon has several possible explanations. For typical residential exposures, the estimated excess risk from studies of the miners is small, with RRs in the range of 1.1–1.4, and thus difficult to detect epidemiologically. Subjects typically lived in several homes during their lifetimes, thereby narrowing the range of exposures in the target population and reducing the power of the study. The consequences of residential mobility can be demonstrated with an extreme example. If every member of the population moved every day and if radon levels in homes were statistically independent, the total exposure for each subject after, say, 25 years would be approximately 25 times the mean exposure rate and there would be little or no exposure variation in the population, thus essentially precluding the detection of any risk. Finally, because of methodological limitations, past exposures of individuals to radon progeny are estimated with extreme imprecision.

Lubin *et al. (15)* have discussed mobility and exposure errors and have provided summary tabulations of their implications for the size and power of studies. For example, to maintain adequate power of the study to detect a non-zero excess risk from exposure, a case-control study in which radon exposures are estimated with error may require 10–15 times the number of cases needed when exposure error is absent. Similarly, a study of subjects who live in an average of three homes in their adult lives would require about three times the number of study subjects, as a study in which subjects live in a single home.

ERRORS IN EXPOSURE

We first address exposure assessment error. Pierce *et al. (16)* have considered some of these issues in an informative discussion of errors and their effects on the estimation of the radiation dose–response relationship in the Japanese atomic bomb survivors. Their goal was an estimate of the "true" dose–response relationship, accounting for errors in dosimetry. In our report, we evaluate the effects of errors in exposures in light of current epidemiological findings. Since information on the distributional properties of errors in the assessment of residential exposure is currently lacking, any adjustment of observed dose–response patterns in residential studies using various error models would be highly speculative at this time.

The pattern of lung cancer risk in miners indicates that exposures in the 5–30-year period prior to the current time have a stronger effect than earlier exposures on lung cancer risk associated with radon *(1, 2)*. This temporal pattern has allowed investigators to restrict exposure assessment in case-control studies to a limited window of time (which will be referred to as the exposure-time window) prior to time of study enrollment. This is fortunate, since it is often impossible to locate residences and measure radon concentrations for homes in which subjects have lived many years in the past. However, if exposures more than 30 years prior to time of enrollment do contribute to lung cancer risk, then ignoring these exposures by design adds imprecision to the exposure estimates *(15)*. To simplify this analysis, we assume that the biologically relevant exposure period is the 25-year window, from 5 to 30 years prior to the current time, ignoring exposures in the most recent 5 years, because immediate exposures are unlikely to be causally related to a lung cancer. In the initial simulations we assume that subjects live in a single home during the exposure period of the previous 5–30 years, but then relax the assumption to assess the consequences of mobility.

It is important to distinguish between error in the measurement device and error in assessment of individual expo-

TABLE II
Sources of Error in the Estimation of Cumulative Indoor Radon-Progeny Exposure

Errors related to measurement of radon
Measurement error in the α-particle track device
Measurement at one fixed location in a room
Measurements limited to one or two rooms only
Mis-specification in time of placement of detector
Use of contemporary measurements to characterize past levels
Sources of error in duration of exposure
Variation of percentage occupancy over time
Imprecision of percentage occupancy
Exposures outside the subject's home
Measurement gaps for homes within the exposure period and imputation of missing data
Exposure as duration times mean exposure rate as an approximation of the time-integrated exposure rate
Equilibrium and conversion of radon concentration to WL [a]
Temporal and other variation in the relationship between exposure and dose

[a] WL denotes working levels, the unit of radon progeny measured in studies of underground mines.

sure. The most common area dosimeter used in epidemiological radon studies is the α-particle track detector *(17, 18).* Radon concentration is determined by counting the number of etched tracks made on plastic film by α particles. Both the counting and measurement processes are subject to error, which has been estimated to be about 15–25% *(8, 19).* This level of error in the measurement process thus defines the lower bound for the accuracy of any assessment of exposure to radon progeny based on α-particle track devices.

Many other factors contribute to error in the estimation of personal exposure (Table II). Total personal exposure to radon progeny is the summation of exposures received in all environments, including the home, the workplace and outdoors. Alpha-particle track detectors are usually left in place for several months to a full year (Table I). In some studies, concentration measurements from short-term (3–7 days) devices supplemented long-term devices. The short-term measurements were used if a long-term device was lost or unusable, although data from short-term devices typically accounted for only a small proportion of the total measurements in the major studies. Residential radon concentrations vary daily and seasonally,[2] with winter levels as much as fourfold higher than summer levels *(20),* and therefore short-term measurements or single-season measurements may not provide an accurate characterization of year-long radon levels. In addition, short-term measurements have greater variability, thereby increasing error in exposure assessment and decreasing power of the study *(21).*

Surveys of U.S. homes have found that radon concentrations are generally consistent with a log-normal distribution with geometric mean (GM) 24.8 Bq m^{-3} and geometric standard deviation (GSD) 3.11 *(22, 23).* For comparison with the miner studies, we present cumulative exposure in units of working level months (WLM).[3] Assuming no residential mobility and standard adjustments for occupancy and equilibrium levels for radon and its decay products, cumulative residential exposure over 25 years would be approximately log-normally distributed with GM 3 WLM and GSD 3.11.

In analyses of indoor radon studies, exposure in the defined time window is usually computed as either the time-weighted average concentration (TWAC) or cumulative exposure in Bq m^{-3}-years. For TWAC, gaps in the measurement data for previous homes are often ignored when there is more than one residence. For example, if one subject lived for 30 years in a home measured at 150 Bq m^{-3} and a second subject lived for 15 years in a home measured at the same level and 15 years in an unmeasured home, then in the absence of an imputed concentration for the unmeasured house, each subject would have a computed TWAC of 150 Bq m^{-3}. However, because of regression toward the mean, the TWAC for the latter subject is likely an overestimate. Thus, if coverage of the exposure-time window is related to case status, ignoring measurement gaps is potentially biasing. Unless there is nearly complete coverage of the exposure-time window, imputation of missing data, with the appropriate adjustment for the variance estimates of parameters, would be the preferred approach *(24).*

Cumulative exposure is the time integration of exposure rate over the exposure period. However, in most epidemiological studies, cumulative exposure is computed as the summation for all homes occupied during the exposure-time window of the product of radon concentration and duration of occupancy in the home, with missing measurement data replaced by imputation procedures. Both concentration and occupancy are determined imprecisely and the summation is

[2] G. A. Swedjemark, *Radon and its Decay Products in Housing. Estimation of the Radon Daughter Exposure to the Swedish Population and Methods for Evaluation of the Uncertainties in Annual Averages.* Doctoral Dissertation, Department of Radiation Physics, University of Stockholm, 1985.

[3] One working level (WL) equals any combination of radon progeny in one liter of air which results in the emission of 130,000 MeV of energy from α particles. WLM is the product of time, in units of 170 h, and WL. Indoor radon is measured in becquerels per cubic meter, Bq m^{-3} (or picocuries per liter, pCi l^{-1}), the number of atomic decays per liter of air. In U.S. homes, the average radon concentration is about 46.3 Bq m^{-3} (1.25 pCi/1) and median concentration is 24.8 Bq/m^3 (0.67 pCi 1^{-1}). With 70% occupancy and standard housing conditions, 1 year of residence at 37 Bq m^{-3} results in approximately 0.2 WLM.

therefore only an approximation of the true time integration. Only current radon levels can be measured, and current levels may differ substantially from levels 15–30 years previously, due to tightening of homes for energy conservation or other modifications *(25)*. In addition, measurements are typically made only in a few rooms, and no measurements of potential sources of exposure outside the home are made. Finally, occupancy time in homes is uncertain and likely varies with the age and employment status of an individual.

To formalize our discussion of errors in exposure, suppose that subjects live in a single residence, that X denotes the true but unmeasured exposure, and that ln (X) is normally distributed with mean μ and variance σ^2, written $X \sim LN[\mu,\sigma^2]$. As noted by Pierce *et al. (16)*, X is not a random variable, but represents a fixed exposure, and its "distribution" reflects the range of values in the population. Due to errors, X cannot be measured directly. Instead, we assume that $Z = X \times U$ is observed, where U is a multiplicative exposure error. It is assumed that U is log-normally distributed with ln (U) having mean 0 and variance τ^2, i.e., $U \sim LN[0,\tau^2]$, and is independent of the joint distribution of X and disease status. As a result of these assumptions, Z is also log-normally distributed, $Z \sim LN[\mu,\sigma^2+\tau^2]$.

Although a close relationship between X and Z is desired, it is important to distinguish between the conditional distribution of the true exposure given the observed exposure, $X|Z$, and the observed exposure given the true exposure, $Z|X$. Under the assumptions described above, both conditional probabilities are log-normally distributed. For a given value of the true exposure $X = x$, we have $Z|X = x \sim LN[\ln(x), \tau^2]$ and for a particular observed exposure $Z = z$, $X|Z = z \sim LN[\mu + (\ln(z) - \mu)/(1 + \tau^2/\sigma^2), \sigma^2\tau^2/(\tau^2+\sigma^2)]$.

For the distribution $Z|X = x$, an unbiased exposure error implies that the expectation of observed exposures Z is x. However, in our context unbiasedness occurs only on the logarithm scale; i.e., for the distribution $Z|X = x$ the expectation of the transformed ln (Z) is ln (x) for each $X = x$. On the original scale of measurement, Z is not unbiased. The median of the $Z|X = x$ distribution is x, while its expectation is $x \times \exp(0.5\ \tau^2)$, which exceeds x, and is thus unbiased only when $\tau^2 = 0$ and exposure is known exactly. Moreover, the variance of the observed exposure increases with the true exposure, since Var $(ZX = x) = x^2$ Var (U). The distribution of $Z|X$ for various values of τ and x is shown in Fig. 2, where for the X distribution we set $\mu = \ln(3)$ and $\sigma^2 = \{\ln(3.11)\}^2 = 1.3$. In the figure, with X equal to 3.9 and 18 WLM, the means of $Z|X = x$ are 3.3, 9.8 and 19.5 WLM for exp $(\tau) = 1.5$; 3.8, 11.4 and 22.9 WLM for exp $(\tau) = 2.0$; and 5.5, 16.5 and 32.9 WLM for exp $(\tau) = 3.0$, respectively. For example, for a group of individuals with a true exposure of about 18 WLM, their mean observed exposure could be substantially larger.

Case-control studies have the goal of relating lung cancer risk to the true exposure X. For subjects with the same

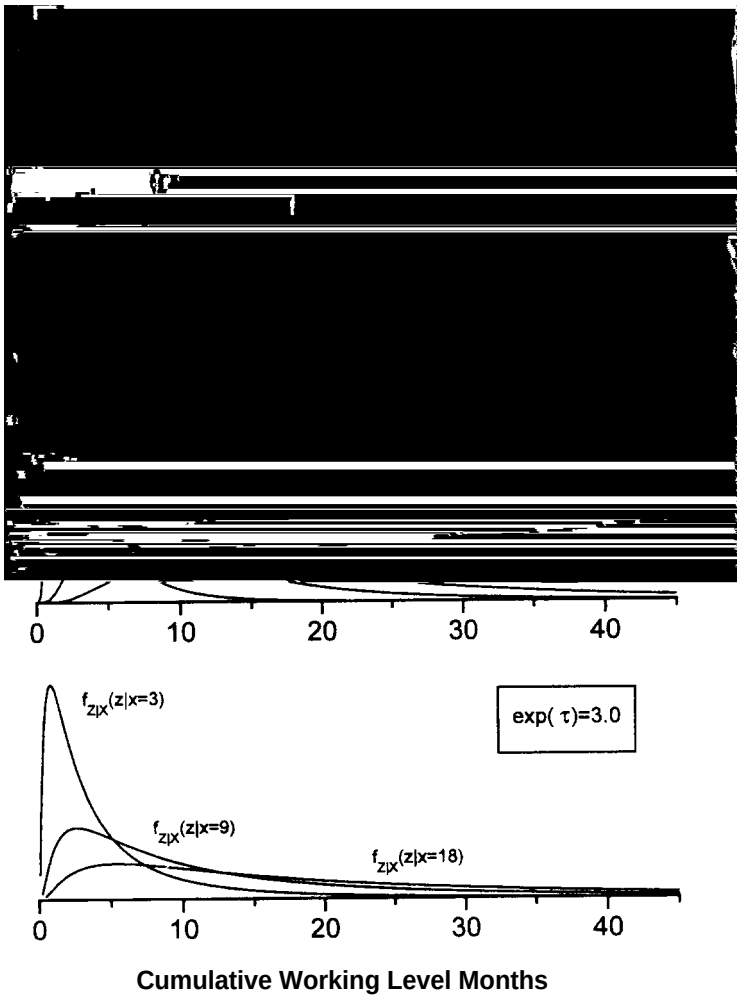


FIG. 2. The distribution of observed cumulative radon exposure (Z) conditional on true exposure (X), denoted $f_{z|x}$, with X taking values 3.9 and 18 WLM, which correspond to 25 years of exposure at 24.8, 74 and 148 Bq m^{-3}, respectively. The distribution of $Z|X$ is log-normal with ln (ZX) having mean μ = ln (x) and variance τ^2.

observed exposure $Z = z$, the distribution of $X|Z = z$ reflects the range of true exposures for subjects with the same observed value. Assuming ln (Z) has mean $\mu = \ln(3)$ and variance $\sigma^2 + \tau^2 = 1.3 + \tau^2$, Fig. 3 shows the $X|Z = z$ distribution for various τ^2 [or exp (τ)] values and for $Z = 3$ WLM and $Z = 18$ WLM, which correspond to 25 years cumulative exposure in a home with radon concentration levels of 24.8 Bq m^{-3} and 148 Bq m^{-3}, respectively. For $Z = 3$ WLM, the median of $X|Z = z$ is 3 WLM, while for $Z = 18$ WLM, medians are 14.7, 11.1 and 7.6 for exp (τ) taking values 1.5, 2.0 and 3.0. respectively. For a given value of $Z = z$, the dotted lines delimit the exponential of one standard deviation above and below the mean (and median) of ln (X), i.e. $\exp[\mu + (\ln(z) - \mu)/(1 + \tau^2/\sigma^2) - \sigma\tau/(\tau^2 + \sigma^2)^{1/2}]$ and $\exp[\mu + (\ln(z) - \mu)/(1 + \tau^2/\sigma^2) + \sigma\tau/(\tau^2 + \sigma^2)^{1/2}]$.

When exposure is determined with error, an observed exposure above the true median exposure more likely overestimates than underestimates the true exposure. The

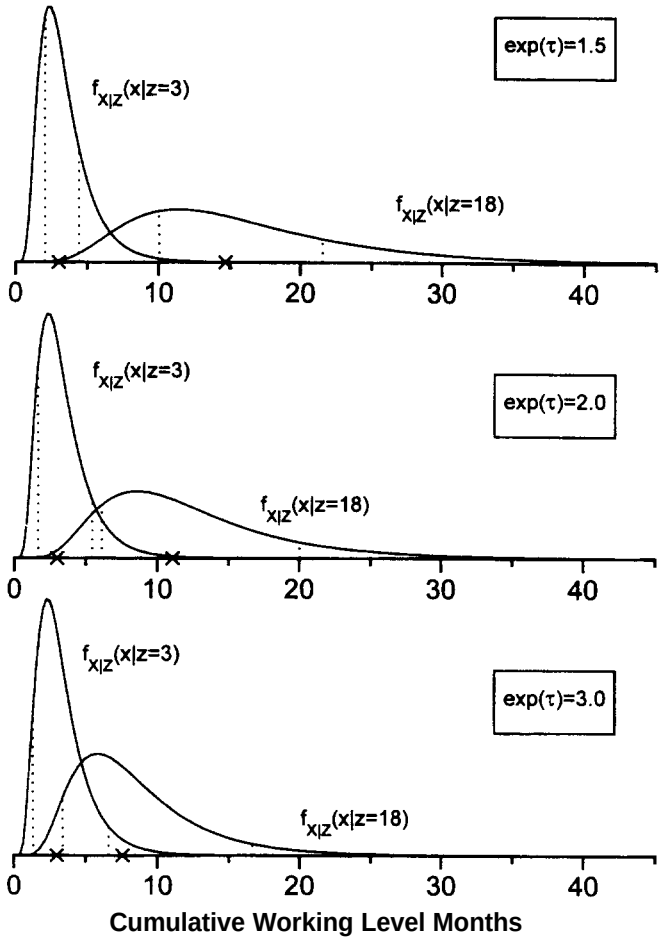


FIG. 3. The distribution of true cumulative radon exposure *(X)* conditional on observed exposure *(Z).* denoted f_{x} with Z taking values 3 and 18 WLM, which correspond to 25 years of exposure at 24.8 and 148 Bq m^{-3}, respectively. Crosses denote median of the *XZ* distribution [or mean of the ln *(XZ)* distribution] and dotted lines denote one standard deviation (on the log scale) from the median.

median for the true exposure is always between exp (μ), the median of the true exposure distribution *X,* and the observed $Z = z$. The median of the $X|Z = z$ distribution can be written $z \times e^{K}$, where $K = [\tau^2 \ln (e^{\mu}/z)/(\tau^2 + \sigma^2)]$. For $z > e^{\mu}$, $K < 0$ and $z \times e^{K} < z$, while for $z < e^{\mu}$

Error distribution:[a] exp(τ)	Range[b] of true exposure (WLM) $X\|Z$ = 3 WLM	$X\|Z$ = 9 WLM	$X\|Z$ = 18 WLM
1.0	3.0	9.0	18.0
1.5	2.1–4.4	5.4–11.6	10.0–21.5
2.0	1.7–5.4	3.7–12.1	6.1–20.1
3.0	1.4–6.6	2.4–11.7	3.4–16.7

where the RR is a linear function of cumulative radon-progeny exposure *(X)*, and β, the excess RR per unit exposure, and exp (α) is the relative odds of lung cancer *(D* = 1 denoting lung cancer and *D* = 0 denoting no lung cancer). For these simulations, β was set equal to 0.0150, which may be an extreme estimate of the excess RR per WLM from data for miners *(2)*, but one that is commonly used for the design of indoor radon studies, and *X* was expressed as radon-progeny exposure by multiplying radon concentration in Bq m^{-3} by (0.18/37) × 25, where the first factor relates Bq m^{-3} in the home to WLM/year under standard assumptions and the second factor represents 25 years of exposure.

In residential studies, at *X* = 0 model (1) defines the risk of disease for individuals with "zero" indoor radon exposure. Although nonexposure has probability zero under a log-normal distribution, β remains a well-defined dose–response parameter which specifies the increase the excess RR for each unit increase in exposure.

We generate data for case-control studies using the following steps.

1. For an individual, generate radon-progeny exposure by randomly sampling from a log-normal distribution with GM 24.8 Bq m^{-3} and GSD 3.11 and converting to radon-progeny exposure in WLM based on 25 years of exposure.
2. From Eq. (l), determine the probability of lung cancer, then randomly sample from a uniform zero-one distribution, to specify disease status *D*.
3. Incorporate an error, *U*, into exposure by randomly sampling from a log-normal distribution with parameters 0 and the specified τ^2, and computing $Z = X \times U$.
4. Repeat steps 1–3 10,000 times.
5. Randomly select 700 disease cases and 700 controls, categorize radon concentration, compute RRs, and compute score tests for trend and homogeneity, using continuous radon concentration as the quantitative variable.
6. Repeat steps 1–5 for the required number of case-control data sets.

The error distribution was specified by setting exp (τ) to 1.0 (no error), 1.5, 2.0 and 3.0. For a log-normal distribution with parameters 0 and τ^2, the standard deviation is $[\exp(\tau^2)\{\exp(\tau^2) - 1\}]^{1/2}$, which can be roughly approximated by exp (τ) - 1. The values for exp (τ) therefore roughly correspond to exposure errors of 0, 50, 100 and 200%, respectively. For ease of comparison with current case-control studies, radon-progeny exposures were rescaled based on 25 years of exposure to radon concentration and RRs were computed by categories of Bq m^{-3}.

Figure 4 shows RRs for 10 simulated case-control studies for each of four different error distributions. Tables of the RRs plotted in this figure are available on request from the authors. For comparison with existing indoor radon studies, the axes in Figs. 1 and 4 are the same. The panel with exp (τ) = 1.0 shows results for exposure measured without error and demonstrates the natural variation in studies. Even for a relatively large study of 700 cases and 700 controls, the range of possible RRs in a single study can be substantial. With radon concentrations as described above, 25 years of residency, no mobility and exposure measured without error, a study with 700 cases and 700 controls has 47% power of detecting an excess risk, based on an excess relative risk of 0.015/WLM and using the formulae in ref. *(15)*. In line with this calculation, among the 10 simulated studies with exp (τ) = 1.0, the null hypothesis of no trend in the RR with radon concentration was rejected in 4 of the 10 data sets. Thus, due to chance alone, 6 of 10 studies would not link radon to lung cancer even though an underlying radon effect was present in the population. Other panels of the figure show results with varying degrees of exposure error. The combined dotted-dashed lines show the theoretical exposure–response relationship with error-prone exposures. With error in exposure, the observed exposure response is convex from below. For increasing error, the gradient of the RR decreases with increasing cumulative exposure. Moreover, the power to reject the null hypothesis of no trend in the RRs decreases; with exp (τ) = 2.0 3 studies had a significant test of trend, while with exp (τ) = 3.0 no study rejected the null hypothesis.

For each error parameter, data from the first 5 "studies" were pooled, giving a total of 3,500 cases and an equal number of controls. For the four error parameters, tests of no linear trend were rejected for exp (τ) = 1.0, 1.5 and 2.0, while *P* = 0.05 for the test of no linear trend with exp (τ) = 3.0. When all 10 "studies" were pooled, the test of no linear trend was rejected for all error parameters.

We next consider more realistic situations for the effects of errors, residential mobility and incomplete coverage of the exposure-time window due to unmeasured houses on the statistical test of no effect of indoor radon. Table IV shows the percentage of times out of 1,000 simulated case-control studies that the null hypothesis of no trend in the RR with increasing radon exposure was rejected using a two-sided alpha-level test of 0.05 under various exposure assessment conditions, i.e. the empirical power derived through simulation. For example, a case-control study with 700 cases and 700 controls and with all subjects residing in a single home rejected the null hypothesis of no radon effect using a 0.05-level test about 45% of the time; i.e., the power of the study was about 0.45, similar to the theoretical power of 0.47. Table IV shows that study power declined with increasing exposure error, with powers of 0.29 and 0.17 for exp (τ) = 2.0 and 3.0, respectively.

Table IV also illustrates the effects of residential mobility and partial coverage of the exposure-time window. When all previous houses were measured, results listed

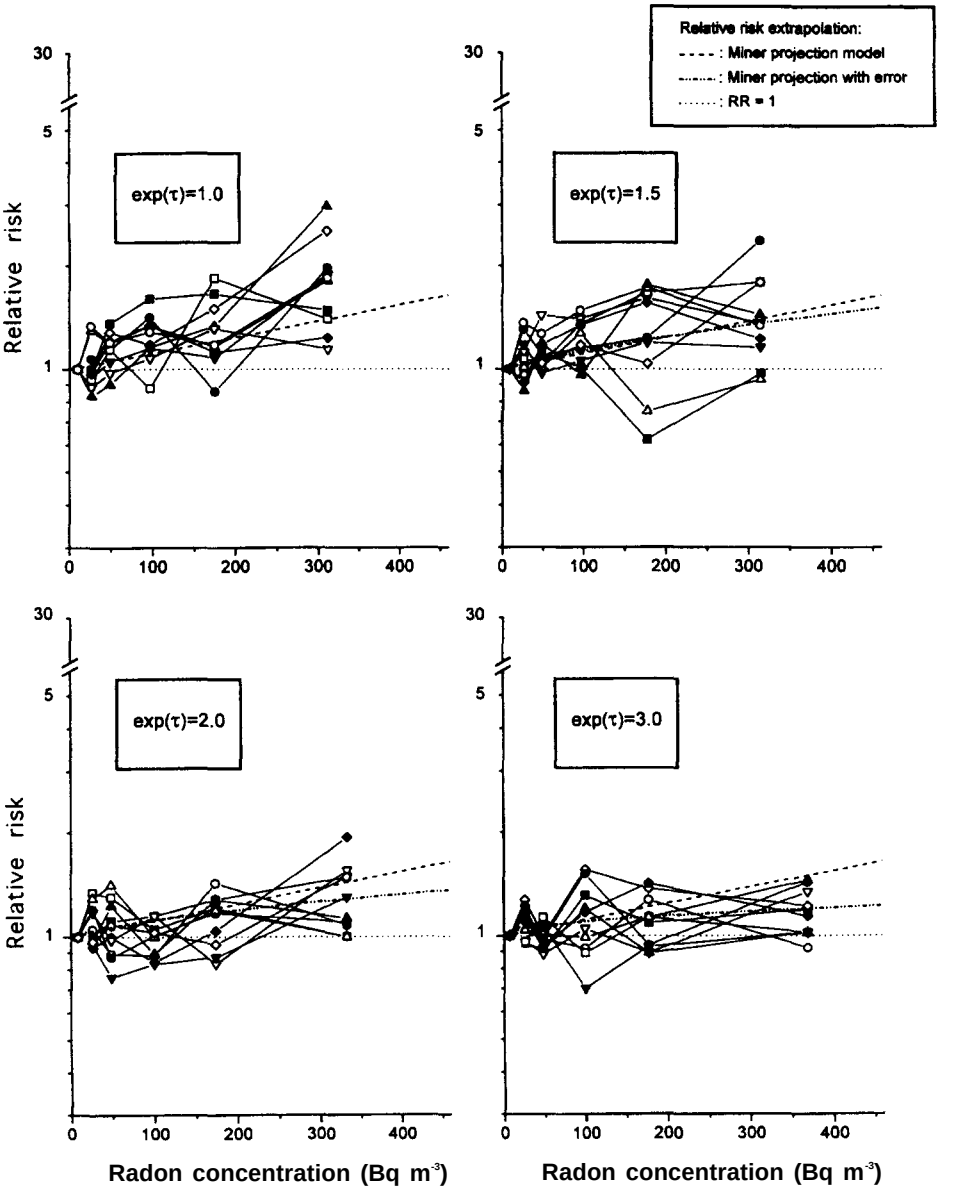


FIG. 4. Relative risks (RR) by categories of Bq m^{-3} for 10 randomly generated case-control studies in which exposures are measured with error. The true radon concentration is distributed log-normally with geometric mean 24.8 Bq m^{-3} and geometric standard deviation 3.11. Duration of exposure is taken as 25 years. A multiplicative error distribution is assumed log-normal with parameters 0 and τ^2. The value exp $(\tau) = 1.0$ denotes exposures measured without error. Scales of the axes are the same as for Fig. 1.

under columns labeled "100%" show that an increase in the number of residences decreased the power of the study, due to a narrowing of the range of exposures. With no exposure error, i.e. exp $(\tau) = 1.0$, power declined from 0.45 to 0.31 to 0.28, for one, two and three residences, respectively. Incomplete coverage of the exposure-time window reduced the power of the study further.

In residential radon studies reported to date, radon measurements in homes covered about 50–75% of the exposure-time window. For our simulations, it was assumed that for multiple residences, subjects lived an equal length of time in each house; i.e., for two and three residences subjects lived 12.5 years or 8.3 years in each house, respectively. In these simulations, unmeasured houses were ignored and TWAC was computed based on available data. Table IV shows that for two residences, 50% coverage of the exposure-time window caused about a 40% drop in power. For three houses, 67% coverage resulted in a smaller loss of power, although

TABLE IV

The Percentage of Times the *P* Value for the Score Test of No Linear Trend in Relative Risk with Exposure Is Less than 0.05, Based on 1,000 Simulated Case-Control Studies[a]

Error distribution:[c] exp(τ)	Number of homes occupied in 5–30-year exposure window[b]					
	1	2		3		
	Percentage coverage of exposure-time window					
	100%	100%	50%	100%	67%	33%
	Study size: 700 cases and 700 controls					
1.0	45.0	30.6	17.1	28.2	24.2	11.5
1.5	41.4	26.6	16.6	24.9	16.4	10.8
2.0	29.4	18.8	12.7	9.4	9.2	6.8
3.0	17.1	11.8	7.2	6.4	8.6	5.8
	Study size: 2,000 cases and 2,000 controls					
1.0	89.8	73.6	46.0	60.8	52.6	32.1
1.5	84.8	66.8	44.1	55.1	42.1	29.4
2.0	71.0	54.0	35.6	34.4	26.6	23.5
3.0	40.8	32.9	22.0	23.6	14.6	13.0

[a]Risk is based on a 0.10 background rate of lung cancer and an excess relative risk of 0.015 per working level month. Exposure is based on 25 years of residence and a log-normal radon concentration distribution with geometric mean 24.8 Bq m^{-3} and geometric standard deviation 3.11.

[b]For multiple homes, it is assumed that equal numbers of years are spent in each home. Thus, for two homes, 50% indicates that 12.5 years of the exposure-time window was covered by radon measurement data, while for three homes, 33% and 67% indicate that 8.3 and 16.7 years of the exposure window were covered by measurement data, respectively.

[c]The multiplicative error distribution is assumed to be log-normal, with the logarithm of the error having mean 0 and variance τ^2. The row with $\exp(\tau) = 1$ shows results when exposure is measured without error.

power was already affected substantially due to increased mobility. The simulations also suggest that some, albeit modest, improvement in power could be achieved with the use of imputation procedures for missing data.

The simulations of the empirical power were repeated with hypothetical studies of size 2,000 cases and 2,000 controls. Table IV shows that power was increased markedly with larger study sizes, but with realistic exposure errors and more than one residence, power to detect a nonsignificant effect was still only 0.20–0.30.

A final group of simulations was conducted to evaluate the effects of error and residential mobility on the distribution of estimates of β. Using 700 cases and 700 controls, we generated 500 studies under a model that assumed no effect for exposure, $\beta = 0.0$, and 500 studies under a model with $\beta = 0.015$, and estimated the dose–response parameter for each set of data. We assumed complete coverage of the exposure-time window. Figure 5 shows results of simulations in which we assumed subjects lived in 1, 2 or 3 houses and with $\exp(\tau) = 1.0$, 2.0 and 3.0. Several patterns are apparent. Since the estimation procedure is unbiased, distributions of the estimates for the simulations with $\beta = 0.0$ (hatched bars) are centered at zero for each set of parameters. For $\beta = 0.015$, distributions of estimates (solid bars) are centered at 0.015 only when there is no exposure error; with exposure error, the distributions of estimates are centered at lower values as error increases, illustrating the attenuation of the observed dose–response estimates. For each error distribution and for $\beta = 0.0$ or $\beta = 0.015$, increasing residential mobility narrows the ranges of exposures in the population and thereby increases the variability and spread in the estimates of β (Fig. 5, rows). For a fixed numbers of houses, variability of the estimates decreases with increasing error, due to an increase in the range of observed exposures (for fixed true exposures, as illustrated in Fig. 2) (Fig. 5, columns). Figure 5 also shows the increasing overlap of the distributions of the dose–response estimates based on $\beta = 0.0$ and $\beta = 0.015$ as exposure error and residential mobility increased. Figure 5 demonstrates the power of the study and effects of error and mobility. The amount of overlap of the distributions highlights the difficulty of using risk estimates from one or a few studies to distinguish an underlying risk of 0.015 per WLM from no radon risk.

A summary of results in Fig. 5 and for incomplete coverage of the exposure-time window is given in Table V. With $\beta = 0.0$, due to chance alone and because of dose–response attenuation, a moderate degree of error results in only 5–10% of studies with 700 cases and 700 controls estimating a dose–response relationship for indoor radon exposure and lung cancer as extreme as 0.010 [an approximate lower limit for the BEIR IV estimate of 0.015 for the constant excess RR model *(2)*]. Note that the absence of symmetry for the number of estimates more

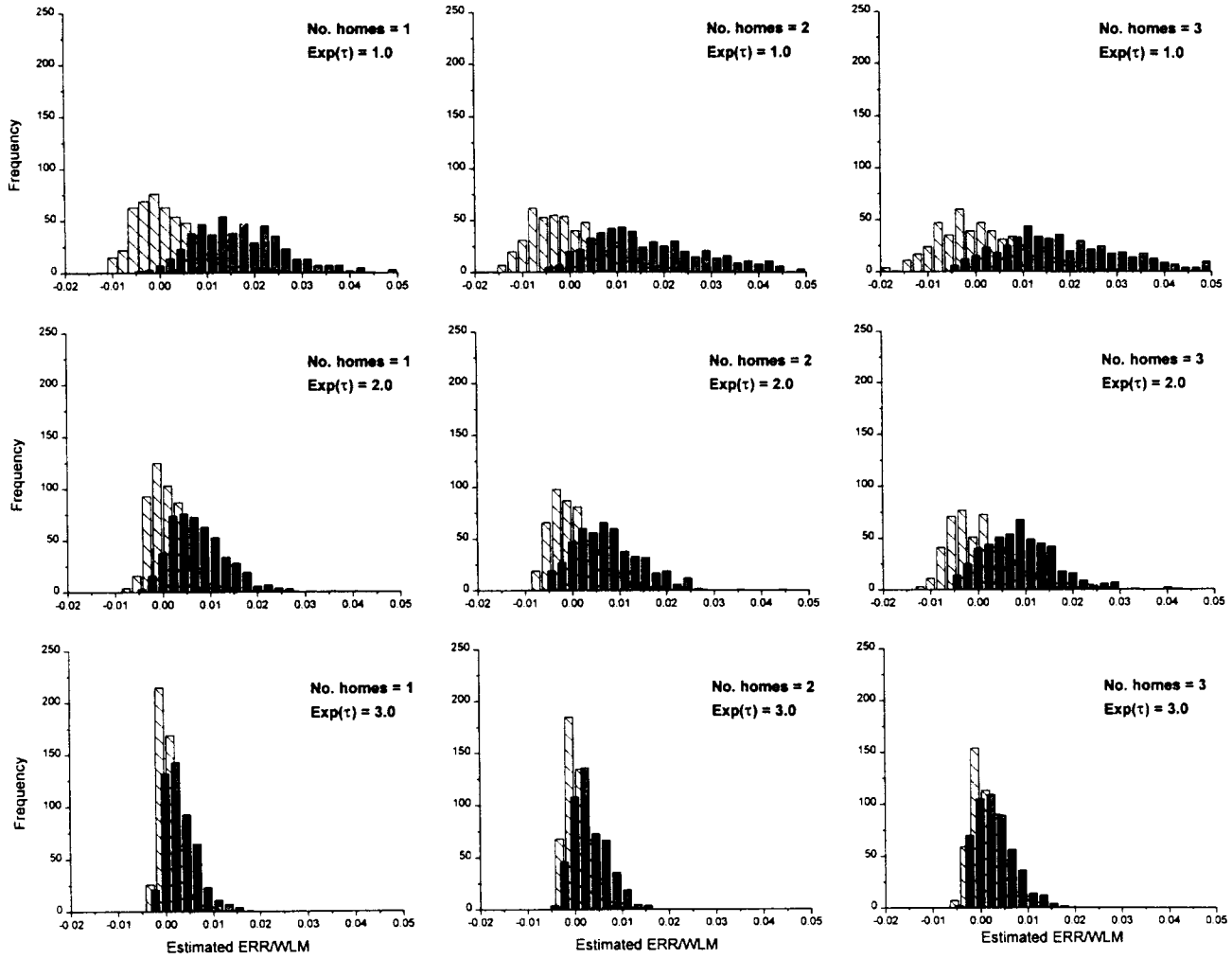


FIG. 5. Frequency distributions of estimates of the excess relative risk per WLM (β) from 500 simulations using a null model of no effect of radon exposure (β = 0.0) (hatched bars) and from 500 simulations using a model with β = 0.015 (solid bars). Exposure was based on complete coverage of a 25-year exposure-time window, and a log-normal distribution of radon concentrations with geometric mean 24.8 Bq m^{-3} and geometric standard deviation 3.11.

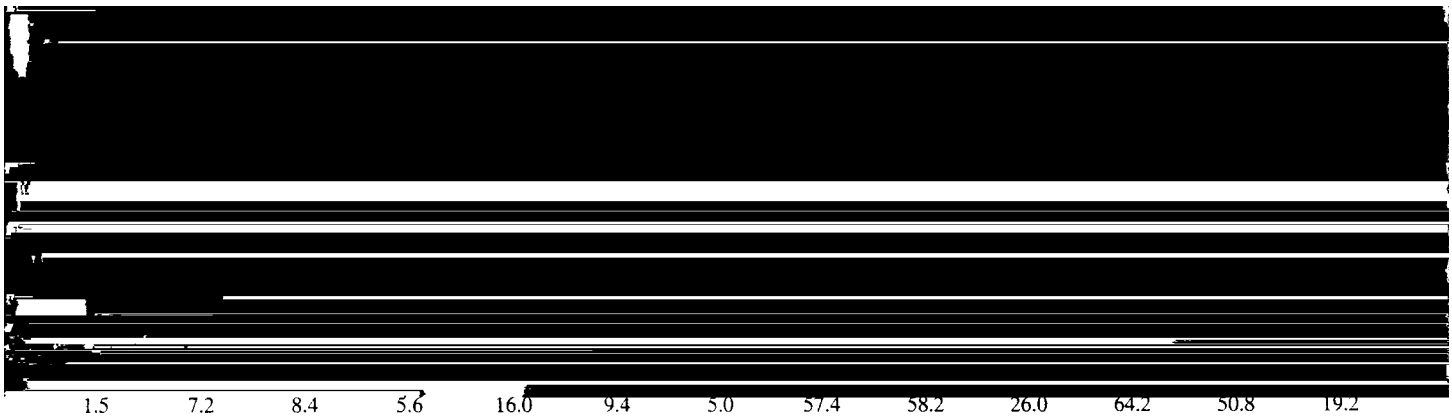
extreme than 0.010 or –0.010 is an artifact of the relatively small sample size of the simulated studies; with 2,000 cases and 2,000 controls, distributions are more symmetrical. With β = 0.015, error and residential mobility result in 15–30% of estimates of 0.0 or less, while 5–15% of estimates are as extreme as 0.010.

The amount of overlap of the distributions of β estimates shown in Fig. 5 is influenced by the distribution of radon concentrations in homes. The simulations were repeated using a radon distribution with GM 60.7 Bq m^{-3} and GSD 2.91, which represents concentrations in Region VIII of the EPA survey, the region with the highest concentrations. (Radon concentrations in Region VIII have an arithmetic mean of 95.8 Bq m^{-3} compared to 46.3 Bq m^{-3} for the U.S. and used in Fig. 5.) While the variability of the β estimates was reduced, the degree of overlap of the distributions for β = 0.0 and β = 0.015 was less than in Fig. 5, but still very substantial (not shown).

SAMPLE SIZES FOR CASE-CONTROL STUDIES

Lubin *et al. (15)* provided a table showing how errors in exposure and population mobility increase required sample size for case-control studies. However, those calculations did not have access to a national probability survey, such as the EPA survey *(22)*, and assumed lifetime exposures, instead of a more appropriate 25-year exposure window. In addition, they characterized error with a less interpretable quantity, denoted f, which was the fraction of the standard deviation of the logarithm of the true exposure, in our current notation τ/σ. Table VI updates the previous sample sizes, showing the number of cases required for a study designed

TABLE V
Summary of Estimates of the Excess Relative Risk per WLM (β) for Data Simulated under the Null Model of No Effect of Radon Exposure (β = 0) and under β = 0.015



1.5	7.2	8.4	5.6	16.0	9.4	5.0	57.4	58.2	26.0	64.2	50.8	19.2
2.0	4.0	7.0	3.4	11.4	5.6	2.6	31.4	32.2	13.6	40.2	30.4	9.4
3.0	0.4	1.2	1.0	2.0	1.0	0.2	4.6	6.0	1.8	6.6	3.4	0.6

Notes. Entries are percentage of estimates out of 500 simulations. Risk is based on a 0.10 background rate of lung cancer and no excess relative risk with working level months.

[a] The multiplicative error distribution is assumed log-normal, with the logarithm of the error having mean 0 and variance τ^2. The row with exp (τ) = 1 shows results when exposure is measured without error. No study is without measurement error and likely realistic situations may be exp (τ) = 2 or 3.

[b] For multiple homes, it is assumed that equal numbers of years are spent in each home. Thus, for two homes, 50% indicates that only 12.5 years of the exposure-time window were covered by radon measurement data, while for three homes, 33% and 67% indicate that 8.3 and 16.7 years of the exposure window were covered by measurement data, respectively.

to have 90% power to reject a null hypothesis based on a 0.05-level test, if the alternative, β = 0.015, were true. For consistency with the simulations, a two-sided hypothesis test was used, in contrast with the calculations in Lubin *et al. (15)* which used a one-sided test. With typical mobility and with exp (τ) about 2.0–3.0, approximately 7,000–18,000 cases and an equal number of controls would be needed, or approximately 5,000–13,000 cases and twice the number of controls. Table VI also shows sample sizes if the true effect were β = 0.010; required sample sizes were almost twofold higher.

TABLE VI
The Effects of Measurement Error, exp (τ), and Mobility on Sample Size[a]

	Mobility pattern			Mobility pattern		
exp(τ)[b]	1 × 25 years	2 × 12.5 years	3 × 8.3 years	1 × 25 years	2 × 12.5 years	3 × 8.3 years
	β = 0.015			β = 0.010		
	Control to case ratio = 1					
1.0	2,033	2,447	3,408	3,848	4,777	6,787
1.5	2,521	3,292	4,879	4,778	6,442	9,743
2.0	3,716	5,365	8,484	7,057	10,525	16,989
3.0	8,429	13,530	22,694	16,038	26,613	45,543
	Control to case ratio = 2					
1.0	1,488	1,810	2,530	2,833	3,545	5,054
1.5	1,846	2,437	3,626	3,519	4,785	7,259
2.0	2,724	3,974	6,311	5,202	7,823	12,667
3.0	6,183	10,034	16,895	11,831	19,797	33,978

Note. Entries are number of lung cancer cases required.

[a] Study required to have 90% power to reject a linear relative risk trend in radon exposure, β = 0, when the true trend is β = 0.015 or β = 0.010, using a two-sided 0.05-level test. Exposure based on 25 years of exposure and occupancy in 1, 2 or 3 houses, with no data imputation.

[b] It is assumed that error is multiplicative and the logarithm of the error is normally distributed with mean 0 and variance τ^2.

These numbers should be interpreted cautiously and as a lower bound, since calculations do not account for unmeasured houses and the adjustment of other risk factors.

DISCUSSION

Accurate exposure estimation is essential for any residential radon study of lung cancer. Estimating past exposures is a formidable task, and a present-day measurement, even if made for an entire year, may not accurately reflect radon concentrations up to 30 or more years ago. Exposure assessment is further burdened by subject mobility, which decreases the range of exposures possible in a population and thereby decreases the power of the study. Mobility also creates the potential for gaps in the reconstruction of prior exposure histories due to an inability to measure all previous houses. Making reasonable assumptions regarding errors, mobility and gaps in the exposure-time window, we find that case-control studies will suffer from so much imprecision in the estimation of radon-progeny exposure that unless there are substantial numbers of cases and controls, any dose–response relationship is more likely than not to be consistent with no exposure effect. Based on these observations, we conclude that the seeming inconsistency among case-control studies to date is in large part an inherent consequence of errors in dosimetry and residential mobility. Moreover, analyses of case-control studies of residential radon exposure could be enhanced by the collection of additional data allowing the estimation of the distribution of exposure error and by the use of statistical methodology that adjusts for exposure error.

Actual studies of indoor radon levels and lung cancer risk are much more complex than our simple computer simulations, which were based only on a simple error structure and residential mobility patterns and were defined by an

studies should be initiated, no matter what the size, unless indoor radon concentrations are high and residential mobility is low or the target population has other special characteristics that address problems of mobility and error. (7) The inconsistency in current studies is also related to low statistical power; i.e. for low relative risks of lung cancer of the order of 1.2, predicted from miner studies, even 1,500 cases would have limited power to detect an effect. (8) Miner-based estimates of risk, despite their own set of limitations, will remain essential in assessing the public health impact of indoor radon.

Received: March 28, 1995; accepted: August 4, 1995

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